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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

Office Action Summary

Application No.	Applicant(s)
08/973,021	rsen, Mouritsen, Hindersson, Duch, Sorensen, Dal
Examiner	**Group Art Unit**
William Sandals	1636

X Responsive to communication(s) filed on *Jan 29, 1998*

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-29* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

Claim(s) _____ is/are allowed.

X Claim(s) *1-29* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

X See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

X Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

X All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

X received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *7, 8 & 10*

Interview Summary, PTO-413

X Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Serial Number: 08/973,021

Art Unit: 1636

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 3 recites a method of producing a random peptide library where the sequence of the random peptide library is made by a procedure of codon split synthesis. There is no description in the specification which describes how one of skill in the art would practice the method, and the prior art does not teach such a method. Split synthesis is an art recognized term, which applies to the chemical synthesis of polypeptides from amino acids, but there is no available teaching on how to practice this method with nucleic acids for production of a coding sequence which could be translated into an peptide or protein sequence, and since the instant Specification is silent on the claimed method, the claimed method is not enabled.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-4, 6-7, 9, 14-22 and 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 recites in line 11, that the transduction and expression of the biologically active nucleic acid or peptide or their cellular ligand has "changed a certain phenotypic trait". It is unclear from the claim which "certain" phenotypic trait is being referred to, and as such is vague and indefinite. Deleting "changed a certain" and inserting --altered a-- would provide be acceptable language.

6. Claim 1, in lines 17-18, recites "synthetic random DNA sequences, in which restrictions upon the randomness may be introduced". Either the DNA is random or it is not random. The claim recites that is random and then recites that it is not random. It appears that the claim intends the latter, but the language is contradictory, and as such is vague and indefinite.

7. Claim 1 recites the limitation "characterized in that". This term is indefinite since it does not provide the skilled practitioner with a clear definition of the metes and bounds of the claimed subject matter. A characterization may not be complete and thorough in its description of a subject, but a mere recitation of an observation or property pertaining to the subject.

8. Regarding claim 1, the phrase "like" renders the claim indefinite because the claim include elements not actually disclosed (those encompassed by "like"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

9. Claim 1 recites the limitation "biologically active ribonucleic acids" in lines 32-33 and 36. There is insufficient antecedent basis for this limitation in the claim.

10. Claim 2 recites the phrase "peptides sequence introduced into or fused to a protein". This language is not art recognized and as such is vague and indefinite.

11. Claims 3 and 4 recite the limitation "random peptide library" in line 2. There is insufficient antecedent basis for this limitation in the claim.

12. Claim 5, line 3, recites a method and uses the expression "by the principle of site directed PCR mutagenesis" to define an intended step in the method. A principle is a theoretical consideration, and is not a step in a method. Deleting "the principle of" would cure this defect.

13. Claims 6 and 7 provides for the use of optimal ligation or combining, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

14. Claims 6 and 7 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

15. Claim 9 appears to claim a Markush group without the proper use of the Markush format.

Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush , 1925 C.D. 126 (Comm'r Pat. 1925).

16. Claim 14 recites the limitation "virus packaging cells" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

17. Claim 15 recites the limitation "new target cells" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 16 recites the limitation "the PBS" in line 4. There is insufficient antecedent basis for this limitation in the claim.

19. Claims 17, 18, 20 and 22 are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

20. Regarding claim 19, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

21. Claim 20 recites the limitation "biologically active protein" in line 2. There is insufficient antecedent basis for this limitation in the claim.

22. Claim 20 recites the limitation "the target protein" in line 4. There is insufficient antecedent basis for this limitation in the claim.

23. Claim 21 recites the limitation "the introduced DNA" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

24. Claim 21 recites the limitation "random peptides" in lines 5 and 6. There is insufficient antecedent basis for this limitation in the claim.

25. Claim 21 recites the limitation "expressed proteins" in line 5. There is insufficient antecedent basis for this limitation in the claim.

26. Claim 22 recites the phrase "DNA sequences are introduced into, or fused to a DNA sequence". This language is not art recognized and as such is vague and indefinite.

27. Claim 24 recites the limitation "derived from". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A derivation of a sequence may be closely patterned after the subject sequence or may be very loosely patterned after the subject sequence, such that it may bear no resemblance or form recognizable as the subject sequence which may be chemically and/or biologically totally unrelated in function or form to the subject sequence.

28. Claims 25-29 provides for the use of biologically active RNA`s or proteins, or t cell epitopes or amino acid sequences or peptides, but, since the claim does not set forth any steps

involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 25-29 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

30. Claims 1-2, 4-5, 8-11, 15-16, 20, 22-24 and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al.

The claims are drawn to a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from: (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to sequences encoding purification tags, (d)

sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a), (b), (c) or (d) are expressed in cells and produce a phenotypic alteration in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule.. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences. The vector may be amplified by PCR prior to the transfection step. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule.

Kay et al. taught (see especially columns 3-6, 16-18, 22-24, and 28) a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from; (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to

sequences encoding purification tags, (d) sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a), (b), (c) or (d) are expressed in cells and produce a phenotypic alteration in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule.. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences. The vector may be amplified by PCR prior to the transfection step. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule. Kay et al. taught each and every aspect of the instant invention, thereby anticipating Applicant's invention.

Claim Rejections - 35 USC § 103

31. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

32. Claims 6-7, 12-14, 17-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. in view of Burke et al and Wong et al.

The claims are drawn to a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from: (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to sequences encoding purification tags, (d) sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a), (b), (c) or (d) are expressed in cells and produce a phenotypic alteration in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis, where the ends of the PCR product may be trimmed by 3'-5' exonuclease. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the

random sequences, where the heterologous ends may contain two different promoters, and where a CMV promoter may replace the 5' LTR. The viral vector may be introduced into the cell by non-viral transfection methods. The vector may be amplified by PCR prior to the transfection step. The host cell may be a viral packaging cell which has been transfected with a vector expressing a single transcript consisting of gag-pol, a drug resistance gene and the env gene. The packaging cell may be a semi-packaging cell line which has been transfected with a minivirus vector. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule. The partly random sequences may encode glycosylation sites or anchor residues, or signal sequences or leader sequences or recognition sequences, which may direct the fusion proteins to defined cellular compartments.

Kay et al. taught (see especially columns 3-6, 16-18, 22-24, and 28) a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from; (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to sequences encoding purification tags, (d) sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a), (b), (c) or (d) are expressed in cells and

produce a phenotypic alteration in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule.. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences. The vector may be amplified by PCR prior to the transfection step. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule.

Kay et al. did not teach that the ends of the PCR product may be trimmed by 3'-5' exonuclease nor that the vectors may contain two different promoters, and where a CMV promoter may replace the 5' LTR. The viral vector may be introduced into the cell by non-viral transfection methods. Also not taught was that the host cell may be a viral packaging cell which has been transfected with a vector expressing a single transcript consisting of gag-pol, a drug

resistance gene and the env gene. The packaging cell may be a semi-packaging cell line which has been transfected with a minivirus vector.

Burke et al. taught (see especially columns 1-6) that the viral vector in an expression library contained random DNA sequences which encoded leader sequences and anchor sequences for fusion proteins, where the sequences were glycosylated and also leader sequences which directed the fusion proteins to specific cellular compartments.

Wong et al. taught (see especially the abstract and introduction, materials and methods and the Figures) the well known use of a 3'-5' exonuclease to blunt end inserts for ligation into a vector, the inclusion of an antibiotic marker gene into a vector and the incorporation of a strong promoter such as the CMV promoter into a viral vector in order to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kay et al., Burke et al and Wong et al. to produce the instant claimed invention because Kay et al. taught the use of a library of random DNA sequences which would act as expressed tags for identification when linked to coding sequences for proteins of interest, or as leader sequences, anchors or sites for post-translational modification. Kay taught the use of viral vectors for the expression libraries, and the use of antibodies and antibody components as fusion proteins with random sequences as described above where the translated proteins and transcribed RNA's were used to detect alterations in the phenotype of the host cell. Burke et al. taught the use of random sequences linked to sequences encoding proteins to produce

fused leader sequences, "tags", and post-transcriptional and post-translational modifications of the fused polypeptides to identify vector induced alterations in the phenotype of the host cell. Wong et al. taught the modification of inserts in viral vectors to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Kay et al., Burke et al and Wong et al. to produce the instant claimed invention because Kay et al. taught the use of a library of random DNA sequences which would act as expressed tags for identification when linked to coding sequences for proteins of interest, or as leader sequences, anchors or sites for post-translational modification. Kay taught the use of viral vectors for the expression libraries, and the use of antibodies and antibody components as fusion proteins with random sequences as described above where the translated proteins and transcribed RNA's were used to detect alterations in the phenotype of the host cell. Burke et al. taught the desirable use of random DNA sequences linked to DNA sequences encoding proteins to produce fused leader sequences, "tags", and post-transcriptional and post-translational modifications of the fused polypeptides to identify vector induced alterations in the phenotype of the host cell. Wong et al. taught the modification of inserts in viral vectors to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell. Since all of the references taught a key element of the instant claimed invention which is the detection of an altered phenotype in a host cell, it would have been obvious to combine these references to produce the instant claimed invention. Further, a person of ordinary

skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Kay et al., Burke et al and Wong et al.

33. Claim 7 rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al, Burke et al. and Wong et al. as applied to claims 6, 12-14, 17-19 and 21 above, and further in view of Lund et al.

The claims are drawn to all the limitations above and to a method of temperature-cycling ligation.

The claims are rejected for all the reasons recited above and because Lund et al. taught (see the entire article) a method of temperature-cycling ligation.

The priority date of the instant claim is the date of filing of the PCT Application No. PCT/DK96/00231, filed May 5, 1996, because upon inspection of the Danish priority document DK0629/95, filed June 2, 1995, no mention of the method of temperature-cycling ligation has been found. The publication date of the Lund et al. reference is March 1, 1996, which establishes this reference as prior art.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kay et al., Burke et al. and Wong et al. with Lund et al. because the Kay et al., Burke et al. and Wong et al. taught the use of ligation chain reaction to amplify a desired DNA prior to insertion of the desired DNA into a vector, and Lund et al. taught

an improved method of use of ligation chain reaction to amplify a desired DNA prior to insertion of the desired DNA into a vector.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Kay et al., Burke et al. and Wong et al. with Lund et al. because the Kay et al., Burke et al. and Wong et al. taught the use of ligation chain reaction to amplify a desired DNA prior to insertion of the desired DNA into a vector, and Lund et al. taught an improved method of use of ligation chain reaction to amplify a desired DNA prior to insertion of the desired DNA into a vector. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Kay et al., Burke et al., Wong et al. and Lund et al.

Conclusion

34. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

September 30, 1998

JAMES KETTER
PRIMARY EXAMINER